

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS & INTERFERENCES**

: 09/742,785

Appl. No.
Applicant : Curatolo et al.
Filed : December 20, 2000
Title: : PHARMACEUTICAL COMPOSITIONS PROVIDING ENHANCED
DRUG CONCENTRATIONS
TC/A.U. : 1618
Examiner : Fubara, Blessing M.
Confirmation No. : 8464
Docket No. : 0003.0565/PC10755
Customer No. : 00152

APPEAL BRIEF

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February 22, 2010

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Real Party in Interest

The real party in interest by virtue of assignment is Bend Research, Inc., an Oregon corporation.

Related Appeals or Interferences

There are no related appeals or interferences.

Status of Claims

Claims 3-28, 30-155 and 157-163 have been cancelled. Claims 1-2, 29, 156 and 164-168 are pending and their final rejection is appealed; a copy of the claims on appeal is set forth in Claims Appendix.

Status of Amendments

All amendments have been entered.

Summary of Claimed Subject Matter

Independent claim 1 is directed to a composition comprising (a) a drug that is a crystalline highly soluble salt form other than the crystalline hydrochloride salt and (b) a concentration-enhancing polymer selected from cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methyl cellulose phthalate (HPMCP) and hydroxypropyl methyl cellulose acetate succinate (HPMCAS). Published Application No. 2002/0006443 ('6443) [0067]-[0071] & [0092]. The drug alone has an aqueous solubility up to about 1 to 2 mg/mL, '6443 [0061] and when it is basic, it has an aqueous solubility of at least twice that of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form. '6443 [0068]. Finally, the composition is not a dispersion '6443 [0031] and the drug and polymer are present as particles in a dry physical mixture. '6443 [0029].

Independent claim 164 differs from claim 1 by specifying that the polymer is HPMCAS alone.

Grounds of Rejection to be Reviewed on Appeal

The issues on appeal are as follows:

- (1) whether claims 1-2, 29 and 167-168 are anticipated under 35 USC §102(b) by Dunn US 4,461,759 (**Dunn**);
- (2) whether claims 1-2, 129, 164 and 167-168 are anticipated under 35 USC §102(b) by Okada et al. US 5,496,561 (**Okada**);
- (3) whether claims 1-2, 29, 156, 164 and 167-168 are anticipated under 35 USC §102(b) by Bymaster et al. US 6,147,072 (**Bymaster**); and
- (4) whether claims 1 and 164-166 are rendered obvious under 35 USC §103(a) by **Dunn** or **Okada** or **Bymaster**.

ARGUMENT

Prior Art Relied Upon

From applicants' standpoint, the most compelling shortcomings of the three prior art references relied upon are as follows. Further shortcomings are discussed *infra*.

Although **Dunn** states that his formulations may contain the drug verapamil or salts thereof, he in fact only discloses formulations of verapamil hydrochloride. See Examples 1-3 at columns 4-5. His formulations may include CAP (Example 3), but when CAP is employed, the drug and CAP are to be granulated together with a bulking agent and/or disintegrant if such are used, and with solvents and then adding the remainder of the ingredients. Column 4, lines 31-38. The patent is silent as to whether the drug and CAP are present as particles in a dry physical mixture.

Okada discloses drug and cellulosic polymer compositions made by either (1) forming a solution of drug, hydroxypropyl cellulose (HPC) and spraying that solution onto spherical sugar pills, then overcoated, typically with Eudragit RS (an acrylic and methacrylic acid copolymer), polysiloxane, silicic acid and glycerine fatty acid ester-containing coating solution (Examples 1-12); or (2) granulating drug and microcrystalline cellulose by extrusion, followed by coating the granules with the same coating solution used in Examples 1-12 (Example 13). Although this patent states that the drug core may be overcoated with a "water insoluble high polymer" such as HPMCAS, HPMCP or CAP (Column 3, lines 36-39 and Column 4, lines 11-13 and 20-23), how to achieve such an overcoating is neither specified nor exemplified.

Bymaster merely recites the known principle that, when it is desired to protect active ingredients from the acidic environment of the stomach, the solid dosage form containing the drug may be coated with a polymer that is insoluble in an acid environment, listing CAP, HPMCP and HPMCAS as examples of such polymers. Column 10, last paragraph. There is no disclosure whatsoever in this patent pertaining to drug and polymer present as particles in a dry physical mixture, and the only composition of the drug ziprasidone is with the hydrochloride salt of the drug duloxetine in a carrier of saturated fatty acid glycerides to form a suppository. Column 13, lines 5-15.

1. Anticipation of Claims 1-2, 29 & 167-168 by Dunn

In order to anticipate, a reference must disclose each and every element of the claimed invention, with those elements arranged in the same way as in the claims. *C.R. Bard, Inc. v. M3 Systems, Inc.*, 48 USPQ 2d 1225, 1230 (Fed Cir 1998). Dunn does not anticipate any of claims 1, 2, 29 or 167-168 for two reasons.

First and most fundamentally, as noted above in the discussion of the shortcomings of Dunn, that patent does not disclose any composition of drug and any of the polymers CAP, CAT, HPMCP or HPMCAS where the drug and polymer are present as particles in a dry physical mixture, as called out in claim 1 and dependent claims 2, 29 and 167-168. Without more, there is no anticipation.

Second, the only form of drug in the Dunn compositions actually made is the hydrochloride salt form. See Dunn Examples 1-3 at columns 4-5. But applicants' claim 1 specifically excludes the hydrochloride salt form of the drug. Claims 2, 29 and 167-168 all depend from claim 1 and so contain this same exclusion.

2. Anticipation of Claims 1-2, 29, 164 & 167-168 by Okada

Okada does not anticipate because it does not disclose any composition of drug and any of the polymers CAP, CAT, HPMCP or HPCAS where the drug and polymer are present as particles in a dry physical mixture, as called for in independent claims 1 and 164 and dependent claims 2, 29 and 167-168.

As noted above in the discussion of the drawbacks of Okada, at best that patent discloses (1) sugar pills coated with a solution of drug and HPC, which are then overcoated with a non-cellulosic polymer (Examples 1-12); and (2) granules of drug and microcrystalline cellulose coated with a non-cellulosic polymer (Example 13). And though Okada states that his drug-containing cores may be coated with a cellulosic polymer such as CAP, HPMCP or HPMCAS, there is not a single specific composition disclosed where this was done, let alone any teaching as to how it could be done.

3. Anticipation of Claims 1-2, 29, 156, 164 & 167-168 by Bymaster

Bymaster does not anticipate any of claims 1-2, 29, 164 & 167-168 because it does not disclose any drug with any polymer present together as particles in a dry physical mixture, let alone the claimed form of drug (crystalline highly soluble salt form other than the hydrochloride salt) or the claimed polymers (CAP, CAT, HPMCP and HPMCAS).

As to claim 156, which is directed to the composition of claim 1 containing the drug ziprasidone, as noted above, the only composition of that drug contains a second drug (duloxetine) in a hydrochloride salt form (excluded by all the rejected claims) in a non-cellulosic carrier of fatty acid glycerides.

4. Obviousness of Claims 1 & 164-166 in view of Dunn or Okada or Bymaster

The Examiner's rationale for this obviousness rejection is unorthodox in the extreme. Specifically, she reasons that each of Dunn, Okada and Bymaster "anticipate" claims 1 and 164, that none of those three patents discloses the salts recited in claims 165-166, but concludes, without citation of any prior art, that all of the salts of claims 165-166 "are known," that the three references contemplate the use of salts of their drugs, and that one of the ordinary skill "would reasonably expect that the compositions of Dunn, Okada or Bymaster could be successfully formulated using the salts of these drugs including those recited in claims 165 and 166 and the enteric polymers to arrive at a product that is at least 2-fold more soluble than the starting salt." Final Rejection, page 10.

The analysis for anticipation is entirely different than that for obviousness, yet the Examiner here apparently argues that anticipation *ipso facto* establishes obviousness. No attempt has been made by the Examiner to provide any rationale why the subject matter of claim 1 or 164 is suggested by Dunn or Okada or Bymaster, which is required for an obviousness rejection. *KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385 (S. Ct. 2007).

As for the Examiner's comment concerning arriving at "a product that is at least 2-fold more soluble than the starting salt," the same is not seen as even being relevant, since there is no reference to any "starting salt," let alone to its solubility in any of claims 1 and 164-166.

Accordingly, this obviousness rejection is not well-founded.

Conclusion

The final rejection of claims 1-2, 29, 156 and 164-168 under 35 U.S.C. §102 and §103 is without merit and should be reversed.

Respectfully submitted,

Date: 2/22/10

A handwritten signature in black ink, appearing to read "Dennis E. Stenzel", written over a horizontal line.

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CLAIMS APPENDIX

1. A composition comprising:

(a) a drug in a pharmaceutically acceptable solubility-improved form that is a crystalline highly soluble salt form other than the crystalline hydrochloride salt; and

(b) a concentration-enhancing polymer selected from the group consisting of cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methyl cellulose phthalate, and hydroxypropyl methyl cellulose acetate succinate

wherein

said drug alone has an aqueous solubility of up to about 1 to 2 mg/mL;

when said drug is basic, said solubility-improved form has an aqueous solubility of at least two-fold the solubility of the more soluble of the crystalline hydrochloride salt and the crystalline free base drug form; and

said composition is not a dispersion and said drug and said polymer are present as particles in a dry physical mixture.

2. The composition of claim 1 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

29. The composition of claim 1 wherein said drug is selected from antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatories, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, and antiviral agents.

156. The composition of claim 1, wherein said drug is ziprasidone.

164. A composition comprising:

(a) a drug in a crystalline highly soluble salt form other than the crystalline hydrochloride salt; and

(b) hydroxypropyl methyl cellulose acetate succinate

wherein

said composition is not a dispersion;

said drug alone has an aqueous solubility up to about 1 to 2 mg/mL;

when said drug is basic, said crystalline highly soluble salt form has an aqueous solubility at least two-fold the solubility of the crystalline hydrochloride salt form; and

said crystalline highly soluble salt form and said hydroxypropylmethyl cellulose acetate succinate are present as particles in a dry physical mixture.

165. The composition of claim 1 or 164 wherein said crystalline highly soluble salt form is selected from the group consisting of the bromide, acetate, iodide, mesylate, phosphate, maleate, citrate, sulfate, tartrate, and lactate salts.

166. The composition of claim 1 or 164 wherein said crystalline highly soluble salt form is selected from the group consisting of the sodium, calcium, potassium, zinc, magnesium, lithium, aluminum, meglumine, diethanolamine, benzathine, choline, and procaine salts.

167. The composition of claim 1 or 164 wherein said drug alone has an aqueous solubility of less than 0.01 mg/mL at pH 1 to 8.

168. The composition of claim 1 or 164 wherein said drug and said polymer are combined without the use of a solvent.

EVIDENCE APPENDIX

Not applicable.

RELATED PROCEEDINGS APPENDIX

Not applicable.